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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/433,777	11/03/1999	JOEL R. HAYNES	APF-18.20	2990

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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/433,777	HAYNES ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26 and 28-47* is/are pending in the application.

4a) Of the above claim(s) *6,8-11,13,14 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,12,15-25 and 29-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's response received on 7/8/03 has been entered. Claims 1-26 and 28-47 are pending in the instant application. Of these, claims 6, 8-11, 13-14, and 26 have been withdrawn from consideration as being drawn to subject matter non-elected without traverse in paper no. 7. Claims 1-5, 7, 12, 15-25, and 29-47 are therefore under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

It is noted that although applicant's have elected the species of "lipid adjuvants" for examination in the instant application, the pending claims have not been amended to reflect the elected subject matter.

Claim Rejections - 35 USC § 112

The rejection of pending claims 1, 16, and 33-47 under 35 U.S.C. 112, first paragraph, for lack of enablement is maintained. Applicant's arguments have been fully

considered but have not been found sufficient in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The rejection of record is concerned with the lack of enablement provided by the specification for shifting the immune response from Th1 to Th2 or vice versa using any lipid adjuvant. The applicant has defined the term "immune shift" as meaning a shift in the immune response from a Th1 response to a Th2 response or vice versa, see specification page 14, lines 19-27. Therefore, by the applicant's own definition of the term, claims reciting an "immune shift" require more than simply generating or enhancing an immune response or a subtype of immune response to an antigen. The term "immune shift" has patentable weight in the claims in terms of enablement, and is particularly claimed in claims 16, and 33-47. Claim 1 has been included in this rejection as claim 16 depends on claim 1. As such, it is proper to consider whether the specification provides an enabling disclosure for this particularly claimed limitation of the instant invention.

The applicant argues that the office has not interpreted the data from example 1 properly. The applicant argues that the results from example 1 clearly show a decrease in the ratio of IgG1 to IgG2 which cannot be explained by an overall reduction in T helper responses. The applicant further argues that the claims do not require the elimination of IgG1, rather all that is required is a "shift" in the immune response favoring one type of response to the other. The applicant also argues that IL-4 secreted from Th2 type cells favors the development of IgG1 while interferon-gamma secreted from Th1 type cells favors the development of IgG2a such that the skilled artisan would understand that a marked increase in IgG2a is the result of a Th1/Th2 switch.

In response, the office maintains that while the applicant's data provided in example 1 shows a decrease in the ratio of IgG1 to IgG2a, the predominant isotype is still associated with a Th2 type response. This does not meet the definition of an "immune shift" provided by the applicant's specification. The previous office action analyzed the working example which uses a lipid adjuvant as follows. The specification provides a working example of the instant invention which demonstrates that co-administration of gold beads coated with monophosphoryl lipid A (MPL) and gold beads coated with a DNA plasmid vector encoding the carcinoembryonic antigen (CEA) under transcriptional control of the CMV promoter to the epidermis of Balb/C mice by particle-mediated bombardment results in a decrease in the ratio of CEA specific IgG1 to IgG2a in mouse serum compared to the administration of CEA-plasmid alone. The specification provides no data concerning the T helper cytokine patterns or level of anti-CEA cytotoxicity in the vaccinated mice. The specification suggests that this decrease in the IgG1/IgG2a ratio correlates to a shift in the T helper phenotype of the mouse's immune response to CEA from a Th2 to a Th1 type response. However, it is clear that the applicant's data does not demonstrate a "shift" from Th2 to Th1 since the overall ratio of IgG1 to IgG2a shows that the predominant isotype is IgG1 rather than IgG2a, which indicates that the primary T helper response is still a Th2 type response. The applicant's data therefore only demonstrates a decrease in the magnitude of the Th2 type helper response rather than an actual shift from predominantly Th2 type isotypes to predominantly Th1 isotypes. The office has not suggested that the an elimination of the Th2 type IgG2a isotypes is required. The office has simply followed the applicant's definition of what constitutes an "immune shift" and applied it to the applicant's data.

Thus, the skilled artisan would not find the specification's working example evidence that the co-administration of MPL shifts the immune response generated against CEA from a Th2 type response to a Th1 type response as the mice continue to exhibit primarily IgG1 anti-CEA antibodies.

Furthermore, the previous office action explained in detail that T helper subsets have not been fully characterized for any species other than mouse, and that it was clearly known in the prior art at the time of filing that different strains of inbred mice appeared to respond differently to antigens in terms of the generation of Th1 versus Th2 responses (Golding et al., Abbas et al.). In analyzing the applicant's working example, the office simply pointed out that the applicant's working example where Balb/C mice were injected with gold beads coated with monophosphoryl lipid A and a plasmid encoding CEA did not in fact demonstrate an "immune shift" from Th1 to Th2, and that based on the known differences in T helper responses to antigen observed in different strains of mice, the skilled artisan would not have been able to predict whether monophosphoryl lipid A would be capable of causing an "immune shift" to an antigen in any species of mouse other than Balb/C or in any other type of mammal. It is also pointed out that the data provided using lipid adjuvants is limited to monophosphoryl lipid A, and that the specification does not provide any data using any other lipid adjuvant or provide an example where the immune response is "shifted" from Th1 to Th2. Claims 1, 16, and 37-47 read broadly on the use of lipid adjuvants which can "shift" the immune responses to either a Th1 type or Th2 type response.

In conclusion, the previous office actions analyzed the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention,

2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by publications from the prior art for the finding of a lack of enablement in the instant. Further, case law including the Marzocchi decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see *In re Marzocchi* 169 USPQ 367, and *Ex parte Sudilovsky* 21 USPQ2d 1702). Finally, the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991).Therefore, due to the art recognized complexity and unpredictability of shifting the T helper immune response to a pathogenic antigen in mammals, the breadth of the claims, and the lack of sufficient guidance from the specification concerning vector and promoter selection, level of antigen expression, genetic background of the mammal to be vaccinated, and routes of administration in regards to their affect on a) generating a particular T helper response in the absence of adjuvant and b) the ability of a particular lipid adjuvant to shift that T helper response to either Th1 or Th2, it would have required undue experimentation to practice the invention as claimed.

Claim Rejections - 35 USC § 102

The rejection of pending claims 1-2, 7, 12, 15, 27-29, 33, 35, 37, 39, 41, 43, and 46-47 under 35 U.S.C. 102 (e) as being anticipated by U.S. Patent No. 5,925,362, hereafter referred to as Spitler et al., is maintained. Applicant's arguments have been fully

considered but have not been found sufficient in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that the office has misconstrued the teachings of Spitler et al., and has used the applicant's specification rather than the Spitler et al. specification to interpret the claims of the Spitler patent. The applicant appears to be arguing that although the Spitler claims encompass the subject matter of applicant's invention, Spitler did not actually contemplate the particular combination of a nucleic acid encoding an antigen and a lipid adjuvant.

In response, as discussed in the previous office action, Claim 1 of the Spitler patent recites a method of eliciting an antitumor immune response to prostate tumors in a subject comprising administering to said subject an active ingredient comprising either human PSA, or an expression system capable of generating in situ said human PSA. Claim 5, which depends on claim 1, clearly recites wherein the active ingredient is formulated to be encapsulated in a liposome or coupled to a liposome and wherein said liposomes optionally contain an adjuvant. Claim 6 also recites the method of claim 1 which further includes at least one adjuvant capable enhancing said antitumor immune response. Claim 7, which depends on claim 6, recites a list of adjuvants which include monophosphoryl lipid A. Since the claims, and in particular, claims 6 and 7, clearly recite the combination of **either** a protein PSA antigen or an expression system capable of generating in situ said PSA and an adjuvant such as monophosphoryl lipid A, there can be no doubt that Spitler et al. contemplated applicant's claimed combination of nucleic acid encoding an antigen and non-DNA adjuvant. If Spitler had intended the adjuvant to be only administered with the protein form of PSA, then claim 6 would have included a

limitation that indicated that the adjuvant would only be administered with the protein form of the antigen. However, claim 6 clearly reads on the administration of the adjuvant with **either** the protein or the nucleic acid form of the PSA antigen. The applicant is further reminded that 35 U.S.C. 282 states that each claim, whether independent or dependant, of an issued U.S. Patent is presumed valid.

In regards to the teachings of the Spitler specification, the applicant states that in columns 7-9 of the Spitler et al. patent, the disclosure refers to the combination of protein/peptide PSA antigens and liposomal adjuvants, and does not actually teach the combination of nucleic acid sequences encoding PSA in combination with non-DNA adjuvants. Based on applicant's analysis of the Spitler specification, the applicant concludes that Spitler never contemplated applicant's claimed combination of nucleic acid and non-DNA adjuvant. This interpretation of the teachings of Spitler et al. is incorrect. Contrary to applicant's analysis of the teachings of columns 7-8, column 8, lines 9-12, clearly states that as an embodiment of the instant invention recombinant vectors included in a liposome injectable "as described above" can be administered to the subject. The description of liposome injectables referenced in column 8, lines 9-12, can be found in column 7 which clearly teaches that liposomes may also include immune system adjuvants such as lipid A. Thus, it is clear from both the teachings of the specification and the claims of the 5,925,362 patent, that Spitler et al. teaches all the elements of the applicant's invention. As such, Spitler et al. anticipates the invention as claimed.

Regarding applicant's argument that the skilled artisan would not combine a DNA vaccine and an adjuvant in a liposome because the DNA vaccine requires transfer into the

nucleus for expression where the adjuvant would not be effective if delivered into the nucleus, at the time of filing, the skilled artisan was well versed in the delivery of DNA to cells using liposomes and was likewise well versed in the use of liposomes to deliver adjuvants. Liposomes, depending on their composition, are fully capable of slow release of their contents to the extracellular space and are also fully capable of introducing their contents into a cell. The liposomes do not directly release their contents into the nucleus, transport into the nucleus from the cytoplasm is dependent on the properties of the released substances. Clearly, since liposomal delivery of DNA leading to DNA expression was well known at the time of filing, the released DNA finds its way to the required location. Thus, applicant's arguments that the skilled artisan would not use a liposome to deliver a DNA and an adjuvant are not persuasive.

In conclusion, the office finds that the claims of the Spitler patent teach each and every element of the claims as required by U.S.C. 102 and that the specification of the Spitler patent supports the subject matter of the Spitler claims. The office also reiterates that 35 U.S.C. 282 states that each claim, whether independent or dependant, of an issued U.S. Patent is presumed valid.

Claim Rejections - 35 USC § 103

The rejection of claims 1, 3-5, 17-25, 29-34, 36-38, 40, 42, 44-45 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,925,362, hereafter referred to as Spitler et al., in view of Fynan et al., Golding et al., and Sedegah et al. is maintained. Applicant's arguments have been fully considered but have not been found sufficient in

overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that the office has not met the requirements set forth in section 2143 of the MPEP for establishing *prima facie* obviousness over the applicant's claimed invention. The applicant's reason for this conclusion is based on applicant's contention that the primary reference Spitler et al. does not teach or suggest applicant's claimed combination of a DNA encoding an antigen and a non-DNA adjuvant. The applicant has not provided any actual arguments traversing the teachings of Fynan, Golding, or Sedegah as applied in the instant rejection. The applicant's arguments concerning the teachings of Spitler et al. are discussed in detail above in the response to applicant's arguments concerning the teachings of Spitler et al. under 35 U.S.C. 102(e). In brief, the office finds that in particular claims 1, and 5-7 of the Spitler et al. patent clearly recite the combination of an expression system encoding a PSA antigen and a non-DNA adjuvant such as monophosphoryl lipid A for use in generating anti-tumor immune responses in vivo in a subject. Therefore, the office submits that the previous office action did in fact follow the three basic requirements for *prima facie* obviousness as required by section 2143 of the MPEP.

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the

application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER